REMARKS

Applicants request reconsideration and then allowance.

The Applicants apreciate the Examiner's courtesy in acknowledging the information (Office Action, page 2) supplied with the prior Response to the requirement for restriction. Applicants respectfully enclose a PTO-1449 type form listing the previously disclosed and considered information. Return of an initialed form is respectfully requested.

The amended specification now includes a "Brief Description of the Drawings" at page 4. The inserted text finds basis in the original specificationat Page 10, starting at line 26, through entire page 11, as well as page 17. This will not limit the scope of any claimed invention.

The amended specification includes clerical identification consistent with administrative "sequence rules." This will not limit the scope of any claimed invention.

It is not presently seen that a substitute specification is required.

The objections to certain claims based on vocabulary (Markush), improperly multiply dependent, and/or for depending from non-elected claims have been addressed. Applicants initially used other claim language that in their view sufficed. It is respectfully submitted that amending the original language to recite colloquial U.S. claim verbiage (Markush or otherwise) shall have no effect on claim scope. Please reconsider and withdraw the objections.

Amended claims 25 and 26 are cast in more conventional method format and Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. § 101. It is not seen that making explict what the claims implicitly concerned will affect claim scope.

The new claims are directed to sub-genuses or species found in original claims 7, 21, 25 and 26. The new claims therefore find basis in the original application and their entry is seen to be in order.

It is respectfully submitted that the May 12, 2003 Response to the requirement for restriction at the very least presented a *de facto* traverse. Applicants respectfully request the Examiner to reconsider and withdraw the requirement for restriction. Attention is respectfully directed to the MPEP 803 direction that all claims should be considered in one application, where at all possible. Any suggestion of a "burden" on searching is not seen as basis for the requirement because the Examiner has had the PCT International Search Report available in the record. In addition, the International Preliminary Examination Report ("IPER") has reported to the public at large that all claims are both novel and, unobvious (having inventive step), and have utility. Another Examiner refused to split the claims and retained all claims in one application as seen from the IPER. Applicants submitted the IPER before the requirement for restriction was interposed so the Examiner herein had the benefit of the International Preliminary Examination Report (IPER). Therefore, Applicants renew their traverse and respectfully request the Examiner to withdraw the requirement for restriction.

Applicants traverse the rejection under 35 U.S.C. §112 (¶1). Applicants respectfully submit claims 1-7, 14 and 16-26 are supported by a written description in the specification that provides enablement for the methods and compounds. The specification enables a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

The peptide of SEQ ID NO: 3 can be used for targeting cells involved in sclerotic and for fibrotic diseases in which the PDGD-receptor is upregulated during disease. Support for this is found at, for instance, page 3.

Applicants respectfully submit that all cells encompassed within the scope of the claims are enabled and that carriers other than albumin can be used for this purpose.

As the Examiner mentions, the application presents examples that cells in the liver can be targeted.

Applicants submit that all cells involved in fibrotic/sclerotic diseases, and in which the PDGF-receptor is specifically upregulated during disease, are targeted by the cyclic peptide conjugates of the invention:

Although Fig. 1a and Fig. 1b show that pPB-HSA (HSA-PDGF-receptor peptide conjugate) is taken up by both normal (healthy) and fibrotic liver organs, there is a clear difference in intrahepatic distribution of pPB-HSA in normal versus diseased liver. In normal liver pPB-HSA is detected in hepatocytes (i.e. parenchymal cells) while in fibrotic liver pPB-HSA is detected in the non-parenchymal cells, namely in the activated HSC. pPB-HSA binds specifically to activated HSC (found in diseased liver) and does not bind to quiescent HSC (found in normal liver). In the patent application intrahepatic targeting of pPB-HSA to the activated HSC in fibrotic liver is shown in Fig. 3-a and Fig. 3-b. As a comparison, Applicants submit Fig. 7 B (B2), which shows that in normal liver pPB-HSA is only detected in the parenchymal hepatocytes and is not detected in the HSC.

Applicants submit literature to substantiate the fact that pPB-HSA only binds to activated HSC. This is consistent with the decision of In re Eynde, 178 U.S.P.Q. (BNA) 470 (CCPA 1973), where the court said:

> That statutory requirement is fulfilled where one possessed of the knowledge had by one skilled in the art could use the invention given the specification disclosure without undue experimentation. A patent applicant may offer evidence, such as patents and publications, to show the knowledge possessed by those skilled in the art and thereby establish that a given specification disclosure is enabling. See, e.g., Martin v. Johnson, 59 CCPA ____, 454 F.2d 746, 172 USPQ 391 (1972). In such a situation, it is the knowledge possessed by those skilled in the art as of the filing date that is of relevance. See Tummers v. Kleimack, 59 CCPA _____, 455 F.2d 566, 568, 172 USPQ 592, 593 (1972).

178 U.S.P.Q. (BNA) at 474. Accordingly, the Examiner is respectfully invited to review Beljaars, Chapter 8, Novel drug carriers for targeting to Hepatic Stellate Cells: new directions for antifibrotic therapies, (1999, thesis, Rijksuniversiteit Groningen), copy

attached, and especially Fig. 6A therein. The difference between activated and quiescent HSC is that in activated HSC the PDGF-receptor is strongly upregulated. As stated at page 177, "[r]esults ...showed that only activated HSC, that display a high PDGFβ receptor expression (6), bound pPB-HSA." Applicants respectfully submit that they have adduced evidence that their specification would have demonstrated to a person skilled in the art that pPB-HSA is specifically targeted to the activated Hepatic Stellate Cells found only in diseased liver, and that targeting of the cyclic peptide-conjugates is therefor dependent on fibrosis.

Next, Applicants respectfully submit Fig. 8, showing that pPB-HSA targets fibrotic kidney cells, and especially glomeruli with high PDGF- ß-receptor expression levels.

Moreover, Applicants submit Fig. 9, showing that pPB-HSA targets diseased kidney cells, having glomerulonephritis (Anti-Thy1 nephritis), characterized by PDGF-receptor upregulation, while not targeting healthy rat kidney cells. Fig. 8 and Fig. 9 provide further evidence that diseased cells, in which the PDGF-receptor is upregulated, are targeted by the cyclic peptides-conjugates of the invention, while healthy cells are not targeted.

Applicants further submit Fig. 10, which is similar to Fig. 4 of the patent application. This figure shows that *in vitro* pPB-HSA binds to the PDGF-receptors of undifferentiated fibroblast cells (used as an *in vitro* model), showing, firstly, that undifferentiated fibroblast cells can be targeted *in vitro* and that, secondly, only pPB-HSA binds to the receptor, while pPB alone does not bind. The reason for this seems to be that the pPB-carrier conjugate mimics the normal ligand PDGF (which is a dimer), while the pPB monomer does not.

Therefore, Applicants respectfully submit their specification and the evidence adduced herewith demonstrate that the originally filed application would have enabled a person skilled in the art so that various cell types (liver, kidney, undifferentiated

fibroblasts *in vitro*) can be targeted using the cyclic peptide conjugates of the invention, and that *in vivo* the cells, in which the PDGF-receptor is upregulated during sclerotic and/or fibrotic disease, are targeted specifically.

Now Applicants also appreciate the Examiner has expressed a view about cyclic peptides and whether or not a HSA carrier can be responsible for targeting and what carriers others other than ablumin, such as human serum albumin, could be used. Applicants respectfully submit that their specification would have enabled a person skilled in the art commensurate with the inventions being claimed and that it enables more than the class defined as human serum albumin.

Applicants submit Fig. 11 (a,b) showing that the cyclic peptide of SEQ ID NO: 3, conjugated to viral carrier particles, targets the viral particles to activated stellate cells, *i.e.* to cells with strongly upregulated PDGF-receptor found within fibrotic tissue. This shows, that indeed the cyclic peptide, and not the HSA, is responsible for targeting and that other carriers than HSA can be linked to the cyclic peptides of the invention for diagnosis or predictive delivery to cells involved in sclerosic and/or fibrosic disease.

Although addressed above, Applicants mention Fig. 9 because it shows that liposomes, into which the conjugates are incorporated, can be used as carriers.

Applicants submission of Fig. 7 though 11 as attachments hereto is without prejudice to their being re-submitted as Exhibits to a Rule 132 Declaration.

If the Examiner has any questions, or desires submission of information in a different format, kindly telephone the undersigned.

Applicants conclude by respectfully, but earnestly, suggesting their application presents an enabling written description that supports claims that are reasonably commensurate in scope and are thus in condition to receive a Notice of Allowance.

Respectfully submited,

FITCH, EVEN, TABIN & FLANNERY

By: _____

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enc.: PTO-1449 Type Form
Figs. 7-11
Beljaars, Chpater 8 (thesis, 1999)

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